TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35.U.S.C. 371

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U S APPLICATION NO
09/673872

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/AU99/00294	20 APRIL 1999	22 APRIL 1998

TITLE OF INVENTION
PHARMACEUTICAL COMPOSITION

APPLICANT(S) FOR DO/EO/US
Tony Wai-Chiu So, Peter Paul Deo, John Tait Russell

Applicant herewith submits to the United States Designated /Elected Office (DO/EO/US) the following items and other information:

1. [x] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. [x] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(I).
4. [ ] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [ ] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [x] Other items or information:

Copy of International Publication WO99/53923 (w/16 pages spec, 4 pages claims)
International Search Report
PCT Request
PCT Demand
International Preliminary Examination Report

09/673872 — 422 Rec'd PCT/PTO 23 OCT 2000

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/AU99/00294	20 APRIL 1999	22 APRIL 1998

17. [X] The following fees are submitted:

CALCULATIONS PTO USE ONLY

Basic National Fee (37 CFR 1.492(a)(1)-(5):

Neither international preliminary examination fee (37 CFR 1.482)

Nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO (1.492(a)(3)) $970.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO (1.492(a)(5) $840.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO(1.492(a)(2)) $690.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) (1.492(a)(1)) $670.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) ..... $ 96.00

ENTER APPROPRIATE BASIC FEE AMOUNT =	$970.00	
Surcharge of $130.00 for furnishing the oath or declaration later than **[ ] 20 [ ] 30** months from the earliest claimed priority date (37 C.F.R. 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate	$	
Total Claims	25 -20=	5	X $ 18.00	$ 90.00	
Independent Claims	2 -3=		X $ 78.00	$	
Multiple dependent claim(s) (if applicable)			+ $260.00	$	
TOTAL OF ABOVE CALCULATIONS =				$1060.00	
Reduction by ½ for filing by small entity, if applicable. **Small Entity Status Claimed** (Note 37 CFR 1.9, 1.27, 1.28).				$ 530.00	
SUBTOTAL =				$ 530.00	
Processing fee of $130.00 for furnishing the English translation later than **[ ] 20 [ ] 30** months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$ 530.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$	
TOTAL FEES ENCLOSED =				$ 530.00	
				Amt. refunded	$
				charged	$

a. [X] A check in the amount of $ 530.00 to cover the above fees is enclosed.

b. [ ] Please charge our Deposit Account No. 02-4377 in amount of $___ to cover the above fees. A copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-4377. A copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

BAKER BOTTS L.L.P.
30 Rockefeller Plaza
New York, New York 10112-4498

Signature: Ronald B. Hildreth

October 20, 2000
Date

19,498
Registration No.

VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) & 1.27(b)) - SMALL BUSINESS CONCERN

Applicant or Patentee: Soltec Research Pty Ltd

Serial or Patent No: _____

Filed or Issued: _____

Title: Pharmaceutical Composition

I hereby declare that I am

☒ the owner of the small business concern identified below;
☐ an official of the small business concern empowered to act on behalf of the concern identified below

NAME OF SMALL BUSINESS CONCERN Soltec Research Pty Ltd

ADDRESS OF SMALL BUSINESS CONCERN 8 Macro Court, Rowville, Victoria 3178, Australia

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.12, and reproduced in 37 CFR 1.9(d), for the purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention described in:

☒ the specification filed herewith with title as listed above
☐ the application identified above
☐ the patent identified above

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organisation having rights in the invention must file separate verified statements averring to their status as small entities, and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a non profit organisation under 37 CFR 1.9(e).

Each person, concern or organisation having any rights in the invention is listed below:

☒ no such person, or organisation exists
☐ each such person, concern or organisation is listed below.

Separate verified statements are required from each named person, concern or organisation having rights to the invention averring to their status as small entities (37 CFR 1.27).

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlements to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardise the validity of the application, any patent issuing therein, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Ross A. MACDONALD

TITLE OF PERSON IF OTHER THAN OWNER MANAGING DIRECTOR

ADDRESS OF PERSON SIGNING 35 MELVILLE ST, HAWTHORN, VICTORIA, AUSTRALIA

SIGNATURE _____ DATE 26 Sept 2000

PHARMACEUTICAL COMPOSITION

Background of the invention

The present invention relates to a vehicle system for a pharmaceutical composition comprising a piperidinopyrimidine derivative. More particularly minoxidil and to a pharmaceutical composition incorporating the vehicle system. Minoxidil is a pharmaceutically active ingredient having several indications including use as a hair growth stimulant.

Minoxidil has poor solubility in water and ethanol and pharmaceutical preparations currently marketed only contain a small percentage of minoxidil. That is, below 5%.

Numerous formulations comprising minoxidil have been published in the prior art including United States patents 4,139,619, 4,820,512, 5,104,646, 5,225,189, 4,938,953, 4,596,812, 5,006,332, 5,156,836 and 5,643,942. Many of the formulations require (or would require where the amount of minoxidil is greater than 5%) a very high percentage (often in the range of 30 to 50%) of propylene glycol or a similar glycol product in order to improve the solubility of minoxidil. Due to the viscosity and tack of propylene glycol, large amounts of propylene glycol or similar agents in a composition are not pharmaceutically or cosmetically elegant and may be unacceptable to the consumer. In addition, high concentrations of propylene glycol may cause local irritation and hypersensitivity upon application to the scalp.

It would accordingly be a significant advance in the art if a composition could be provided which would permit the inclusion of an increased percentage of the active ingredient, but without the disadvantages associated with a high propylene glycol concentration.

Accordingly, it is an object of the present invention to overcome, or at least alleviate, one or more of the difficulties and deficiencies related to the prior art. These and other objects and features of the present invention will be clear from

the following disclosure.

Summary of the invention

Accordingly, the present invention in a first aspect provides a pharmaceutical composition for topical administration, including, as the pharmaceutically active component,

at least 5% by weight, based on the total weight of the composition of a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

an acid in an amount to substantially completely solubilise the piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

a solvent composition including a solvent selected from water and/or a lower alcohol and a co-solvent selected from one or more of the group consisting of aromatic and polyhydric alcohols; wherein when the co-solvent includes propylene glycol, it is present in an amount of less than approximately 10% by weight.

Applicants have surprisingly discovered that by adjusting the acid concentration of the composition the solubility of the piperidinopyrimidine derivatives may be significantly increased without the necessity of utilising large amounts of propylene glycol or optionally by excluding propylene glycol altogether. Accordingly the total amount of active in the composition may be significantly increased. In a preferred form, the pharmaceutically active component is present in amounts of approximately 5 to 25% by weight, preferably approximately 5 to 15% by weight, more preferably approximately 7.5 to 12% by weight.

Preferably the piperidinopyrimidine derivative is minoxidil. Preferably the minoxidil is present in the form of a salt. The salt may include acetate, citrate, succinate, benzoate, hydrochloride, sulphate, phosphate or lactate. Preferably an acetate or lactate salt of minoxidil is used. The acetate or lactate salts may exhibit enhanced solubility and improve the ability to incorporate increased amounts of the active component in the composition.

In a preferred form the acid is added in an amount sufficient to provide an

apparent pH to the composition of approximately 7.0 or less. The apparent pH of the composition is preferably between approximately 5.0 to 7.0, more preferably between 6.0 to 6.5. Any suitable acid may be used to adjust the pH, including mineral acids, such as hydrochloric acid, sulphuric acid, nitric acid and phosphoric acid, or organic acids such as citric acid, acetic acid, succinic acid, or maleic acid, or mixtures thereof. Acetic acid or lactic acid is preferred.

In a preferred form the acid is present at a level that provides at least 0.01 Normal acid. Alternatively, the acid is present in an amount equal to, or greater than, the amount of the piperidinopyrimidine derivative in Normal amounts.

Preferably the lower alcohol is ethanol. The ratio of water to ethanol is preferably from approximately 9:1 to 1;9, more preferably approximately 1:1 to 1:3, by volume.

Preferably, the co-solvent includes benzyl alcohol. The benzyl alcohol may be present in amounts of approximately 2.5 to 95% by weight, preferably approximately 5 to 40% by weight, based on the total weight of the pharmaceutical composition.

Alternatively, or in addition the co-solvent may include a polyhydric alcohol, for example a polyol selected from the group consisting of 1,3-butylene glycol, propylene glycol, preferably glycol 200 (PEG 200), polyethylene glycol 400 (PEG 400), hexylene glycol and dipropylene glycol, or glycerol. When propylene glycol is present, it may be present in amounts of approximately 10% by weight or less, preferably approximately 5% by weight, or less.

In compositions comprising 5% of minoxidil or greater, it is preferred to include benzyl alcohol in the composition. The benzyl alcohol may be present in amounts of up to 85% by weight, based on the total weight of the pharmaceutical composition.

In a preferred form the co-solvent system includes water and benzyl alcohol wherein the benzyl alcohol is in an amount of approximately 40 to 100% by

weight, based on the total weight of the co-solvent system.

In a preferred form the water is present in an amount no greater than 60% by weight.

In a preferred aspect, the pharmaceutical composition includes approximately 5 to 12% by weight, based on the total weight of the composition, of a minoxidil or a minoxidil acid salt;

approximately 88 to 95% by weight of a solvent composition including

approximately 10 to 70% by weight of ethanol,

approximately 2.5 to 85% by weight of benzyl alcohol;

and less than 10% by weight, propylene glycol.

The final presentation of the composition may be any suitable topical pharmaceutical preparation and may include solutions, lotions, ointments, mousses, foams, sprays, aerosols, shampoos and/or conditioners, gels, creams, pastes, and other preparations known in the art. The composition may also include other ingredients such as preservatives, buffers, stabilisers, propellants and the like.

Preferably the pharmaceutical composition is a mousse composition. The mousse composition may include a suitable propellant, for example hydrocarbons or chlorofluorocarbons. Alternatively the pharmaceutical composition may be a gel composition. The gel composition may include a suitable gelling agent, e.g. a cellulose derivative. A hydroxy propyl cellulose, for example that sold under the trade designation Klucel M, has been found to be suitable.

Where an aerosol formulation is used, the aerosol formulation may be a homogeneous, aqueous-alcoholic emulsion system. The aerosol formulation upon actuation produces a stabilized, homogeneous, expandable foam which breaks easily with shear. A composition of this type is sometimes referred to as a "mousse".

In a further preferred aspect, the pharmaceutical composition according to

the present invention may further include an effective amount of a skin penetrating agent.

Suitable skin penetrating agents include alcohols such as dodecanol and oleyl alcohol; amines, such as isopropyl amine, diisopropyl amine, triethyl amine, triethanol amine, diisopropanolamine and ethylene diamine; carboxylic acids, such as oleic acid, linoleic acid and linolenic acid; esters, such as dibutyl sebacate, dibutyl phthalate, butyl benzoate and ethyl caprate; and others, such as Azone, N methyl pyrollidone, bile salts and urea.

All of the compositions herein may be actuated using propellants known per se in the pharmaceutical or cosmetic fields. Such propellants include hydrocarbons such as propane, isobutane or dimethyl ether and chlorofluorocarbons such as P-12, P114, and a 40:60 mixture thereof.

In the pharmaceutical composition according to the present invention, in addition to the above essential components, general purpose components ordinarily used in hair treatment compositions can be formulated, within a range which does not impair the effect of the present invention, including vitamins such as vitamin B.sub.6, vitamin E and derivatives thereof, and biotin; hair generating agents or hair generating aids such as panthothenic acid and derivatives thereof, glycylrrhetic acid and derivatives thereof, nicotinic acid esters such as benzyl nicotinate, cyclosporins, carpronium chloride, cepharanthine, oxendolone, diazoxide, minoxidil, and ethynylesteradiol; antibacterial agents such as hinokitiol, hexachlorophen, phenol, benzalkonium chloride, cetylpyridinium chloride, undecylenic acid, trichlorocarbanilide, and bithionol; refrigerants such as menthol; drugs such as salicylic acid, zinc and derivatives, thereof, and lactic acid and alkyl esters thereof; amino acids such as arginine; oil components such as olive oil, squalane, fluid paraffin, isopropyl myristate, higher fatty acids, and higher alcohols; perfumes; antioxidants; UV-ray absorbers; dyes; humectants; thickeners; perfumes; colour additives and the like.

In a still further aspect of the present invention, there is provided a method for the treatment of hair loss and related indications in humans, which method

includes

providing

a pharmaceutical composition for topical administration, including, as the pharmaceutically active component,

at least 5% by weight, based on the total weight of the composition of a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

an acid in an amount to substantially completely solubilise the piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

a solvent composition including a solvent selected from water and/or a lower alcohol and a co-solvent selected from one or more of the group consisting of aromatic and polyhydric alcohols; wherein when the co-solvent includes propylene glycol, it is present in an amount of less than approximately 10% by weight; and

applying topically to the human scalp a therapeutically or prophylactically effective amount of the pharmaceutical composition.

The hair loss may be related to any of the forms of alopecia including male pattern alopecia. Related indications may include weakening of hair strength, loss of hair colour and the like.

Preferably the pharmaceutically active component includes a minoxidil or a minoxidil salt, more preferably a minoxidil acetate, succinate or citrate salt.

More preferably the pharmaceutical composition includes

approximately 5 to 12% by weight, based on the total weight of the composition, of a minoxidil or a minoxidil acid salt;

approximately 88 to 95% by weight of a solvent composition including

approximately 10 to 70% by weight of ethanol,

approximately 2.5 to 85% by weight of benzyl alcohol;

and less than 10% by weight, propylene glycol.

The present invention will now be more fully described with reference to the accompanying figures and examples. It should be understood, however, that the

description following is illustrative only and should not be taken in any way as a restriction on the generality of the invention described above.

In each of the following examples it was necessary to add an appropriate amount of acid to ensure equivalent acid normality. The standard technique for such an adjustment is to measure the apparent pH of the solution.

In the examples, the apparent pH of each formulation was measured once prepared. The measured taken as the apparent pH due to the high proportion of organic modifiers in the formulations. Typically, 0.5% (w/w) glacial acetic acid (0.1M) would be used in the formulation, which would equate to a pH of 1.0 in an aqueous system when no other components are contributing to the pH of the solution.

EXAMPLE 1

Topical Minoxidil lotion 5% with no propylene glycol

Minoxidil	5.00%
Ethanol	60.3%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	0.6
Purified Water	to total 100%

The apparent pH of the final formulated solution was measured at 6.24.

EXAMPLE 2

Topical Minoxidil mousse 5% for hair treatment

Minoxidil	5.00%
Cetyl Alcohol	2.20%
Stearyl Alcohol	1.00%
Ethanol	51.8
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Propylene Glycol	5.00%
Propellant P75	4.30%
Acetic Acid	qs. pH 6.0
Purified water	to total 100%

EXAMPLE 3

Topical Minoxidil lotion 8% for hair treatment

Minoxidil	8.00%
Ethanol	50.50%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Nitric Acid	qs. pH 6.0
Propylene Glycol	7.30%
Benzyl Alcohol	5.00%
Purified Water	to total 100%

EXAMPLE 4

Topical 8% (w/w) Minoxidil solution

Minoxidil	8.0%
Ethanol	50.5%
Crilet 3	0.4%
Teric 12A4	1.0%
Glacial Acetic Acid	0.3%
Propylene Glycol	7.5%
Benzyl Alcohol	5.0%
Purified Water	to total 100%

The apparent pH of the final formulated solution was measured at 6.24.

EXAMPLE 5

Topical Minoxidil lotion 10% for hair treatment

Minoxidil	10.00%
Ethanol	48.0%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Propylene Glycol	10.0%
Benzyl Alcohol	5.00%
Purified Water	to total 100%

EXAMPLE 6

Topical Minoxidil lotion 10% for hair treatment

Minoxidil	10.00%
Ethanol	47.50%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Benzyl Alcohol	15.00%
Purified Water	to total 100%

EXAMPLE 7

Topical 10% (w/w) Minoxidil solution

	Formulation 3a	Formulation 3b
Minoxidil	10.00%	10.00%
Ethanol	46.80%	44.20%
Crillet 3	0.4%	0.4%
Teric 12A4	1.0%	1.0%
Glacial Acetic Acid	1.0%	0.3%
Propylene Glycol	10.0%	nil
Benzyl Alcohol	5.00%	2.00%
Purified Water	to total 100%	to total 100%

The apparent pH of the final formulated solutions was measured at 6.0 and 6.5 for formulations 3a and 3b, respectively.

EXAMPLE 8

Topical Minoxidil lotion 11% for hair treatment

Minoxidil	11.00%
Ethanol	44.20%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Benzyl Alcohol	20.00%
Purified Water	to total 100%

EXAMPLE 9

Topical Minoxidil lotion 12% for hair treatment

Minoxidil	12.00%
Ethanol	42.7%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Benzyl Alcohol	20.00%
Purified Water	to total 100%

EXAMPLE 10

Topical Minoxidil lotion 12% for hair treatment

Minoxidil	12.00%
Ethanol	42.7%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Benzyl Alcohol	10.00%
Propylene Glycol	10.00%
Purified Water	to total 100%

EXAMPLE 11

Topical Minoxidil lotion 12% for hair treatment

Minoxidil	12.00%
Ethanol	42.7%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Benzyl Alcohol	15.00%
Propylene Glycol	5.00%
Purified Water	to total 100%

There appear to be no obvious gross stability issues associated with any of the formulations. The levels of minoxidil were assayed in formulations 1 and 3a after they had been stored for one and three months at 4°C and 50°C. No measurable loss in potency was observed.

An aqueous gel was prepared by adding 0.75% (w/w) Klucel M (hydroxypropyl cellulose) to Example 4. The viscosity of the gel was measured at

2400 cPoise at 20°C.

EXAMPLE 12

Investigations were carried out to determine which of the components present in Example 7 (10% (w/w) minoxidil solution) were contributing to the solubilisation of minoxidil. The investigation was split into three sections:

- Effect of Co-solvent
- Effect of pH
- Effect of Salt

The solubility determination involved preparation of saturated solutions of minoxidil in the media of interest. These solutions were then filtered (0.45 μm) and analysed against a standard curve by means of direct UV spectroscopy.

Aqueous unbuffered solubility of Minoxidil

The aqueous solubility of minoxidil was found to be 2.2 mg/mL.

Effect of Co-solvent

The solubility of minoxidil was determined in each of the co-solvents, benzyl alcohol, glycerol, propylene glycol and ethanol. Additionally, the solubility of minoxidil was determined in 10% (w/w) solutions of each of the co-solvents, ethanol, propylene glycol and glycerol in water. A 4% (w/w) solution of benzyl alcohol was used since this was found to be the limit of the solubility of benzyl alcohol in water. The following table summarises the results of these studies.

Sample	Minoxidil Solubility (mg/mL)
Benzyl alcohol	125.1
Glycerol	47.3
Propylene Glycol	86.9
Ethanol	18.8
10% (w/w) Ethanol/Water	3.4
10% (w/w) Propylene Glycol/Water	3.0
4% (w/w) Benzyl Alcohol/Water	4.5
10% (w/w) Glycerol/Water	2.7

Analysis indicated that of the systems studied only the use of pure benzyl alcohol would result in the desired 10% (w/w) minoxidil solution.

Effect of apparent pH

Attempts were made to prepare saturated solutions of minoxidil in acetate buffers at apparent pH's 2.5, 3.5, 4.6, 5.0 and 6.0. Saturated solutions were achieved with those pHs above the pKa of minoxidil (4.61), the results of which are summarised in the following table.

pH	Minoxidil Solubility (mg/mL)
6.0	2.5
5.0	4.1
4.6	11.3

It was not possible to determine the solubility limits of minoxidil at pH's below it's pKa, as minoxidil was found to be extremely soluble in acidic media and the buffer used had insufficient capacity to avoid the drift in pH observed with additions of minoxidil to the solution. The maximum minoxidil concentration studied was 22 mg/mL and was found to be completely soluble in pH 2.5 and 3.5 solutions at this concentration. The following table outlines the maximum solubility that would be expected in an acidic aqueous media knowing the solubility of the

base form of minoxidil is 2.2 mg/mL and assuming infinite solubility of the acid form of minoxidil.

pH	Minoxidil Solubility (mg/mL)
3.6	22.0
3.0	87.6
2.6	220.0
2.0	876.0

Effect of Salt

Minoxidil base was used for these studies with the appropriate salt (acetate or HCl) formed *in situ*. As discussed above the use of low pH acetate buffers significantly increased the solubility of minoxidil.

The major factors affecting the solubilisation of minoxidil in an aqueous environment were found to be:

The type and proportion of co-solvents present in the formulation

The pH of the final formulated solution

The amount of minoxidil used

The acid form of minoxidil has been shown to be much more soluble in an aqueous environment. The use of co-solvents has been shown to enhance the solubility of the minoxidil free base. The co-solvents may also enhance the solubility of the acid form. The use of an appropriate salt enhances the solubility of the acid form of minoxidil. Therefore, a combination of these three factors may be used to optimise the solubility of minoxidil in a topical solution based formulation.

All the above examples were stored at room temperature and no crystallisation or precipitation was observed for at least 10 days.

Please note all percentages are based upon the total weight of the

composition unless otherwise specified.

It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

It will also be understood that the term "comprises" (or its grammatical variants) as used in this specification is equivalent to the term "includes" and should not be taken as excluding the presence of other elements or features.

CLAIMS

1. A pharmaceutical composition for topical administration, including, as the pharmaceutically active component,

at least 5% by weight, based on the total weight of the composition of a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

an acid in an amount to substantially completely solubilise the piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof

a solvent composition including a solvent selected from water and/or a lower alcohol and a co-solvent selected from one or more of the group consisting of aromatic and polyhydric alcohols; wherein when the co-solvent includes propylene glycol, it is present in an amount of less than approximately 10% by weight.

2. A pharmaceutical composition according to Claim 1, wherein the acid is added in an amount sufficient to provide an apparent pH to the composition of approximately 7.0 or less.

3. A pharmaceutical composition according to Claim 1, wherein the pharmaceutically active component is present in an amount of from approximately 5 to 25% by weight, based on the total weight of the pharmaceutical composition.

4. A pharmaceutical composition according to Claim 3, wherein the pharmaceutically active component is present in an amount of approximately 7.5 to 12% by weight, based on the total weight of the pharmaceutical composition.

5. A pharmaceutical composition according to Claim 1, wherein the pharmaceutically active component is minoxidil or a salt thereof.

6. A pharmaceutical composition according to Claim 2, wherein the acid provides to the composition an apparent pH in the range of approximately 5.0 to 7.0.

7. A pharmaceutical composition according to Claim 2, wherein the acid is a

mineral or organic acid.

8. A pharmaceutical composition according to Claim 7, wherein the acid includes acetic or lactic acid.

9. A pharmaceutical composition according to Claim 1, wherein the solvent composition includes water and ethanol in a range of approximately 1:1 to 1:3 by volume.

10. A pharmaceutical composition according to Claim 1, wherein the co-solvent includes benzyl alcohol.

11. A pharmaceutical composition according to Claim 1, wherein the solvent composition system includes water and benzyl alcohol wherein the benzyl alcohol is in an amount of approximately 40 to 100% by weight based on the total weight of the co-solvent system.

12. A pharmaceutical composition according to Claim 1, wherein the water is present in an amount no greater than approximately 60% by weight based on the total weight of the co-solvent system.

13. A pharmaceutical composition according to Claim 1, wherein the co-solvent includes an alkylene glycol.

14. A pharmaceutical composition according to Claim 13, wherein the alkylene glycol is selected from one or more of the group consisting of glycerol, 1,3-butylene or propylene glycol.

15. A pharmaceutical composition according to Claim 1, wherein the acid is present at a level that provides at least 0.01 Normal acid.

16. A pharmaceutical composition according to Claim 1, wherein the acid is present in an amount equal to or greater than the amount of the piperidinopyrimidine derivative in Normal amounts.

17. A pharmaceutical composition according to Claim 1, wherein the solvent system includes water and ethanol in a range of approximately 9:1 to 1:9 by volume.

18. A pharmaceutical composition according to Claim 5, wherein the pharmaceutically active component is a minoxidil salt.

19. A pharmaceutical composition according to Claim 18, wherein the minoxidil salt is a minoxidil acetate or lactate salt.

20. A pharmaceutical composition according to Claim 1, including

approximately 5 to 12% by weight, based on the total weight of the composition, of a minoxidil or a minoxidil acid salt;

approximately 88 to 95% by weight of a solvent composition including

approximately 10 to 70% by weight of ethanol,

approximately 2.5 to 85% by weight of benzyl alcohol;

and less than 10% by weight, propylene glycol.

21. A method for the treatment of hair loss and related indications in humans, which method includes

providing

a pharmaceutical composition for topical administration, including, as the pharmaceutically active component,

at least 5% by weight, based on the total weight of the composition of a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

an acid in an amount to substantially completely solubilise the piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

a solvent composition including a solvent selected from water and/or a lower alcohol and a co-solvent selected from one or more of the group consisting of aromatic and polyhydric alcohols; wherein when the co-solvent includes propylene glycol, it is present in an amount of less than approximately 10% by weight; and

applying topically to the human scalp a therapeutically or prophylactically

effective amount of the pharmaceutical composition.

22. A method according to Claim 21, wherein the pharmaceutically active component includes minoxidil or a minoxidil salt.

23. A method according to Claim 22, wherein the minoxidil salt is a minoxidil acetate or lactate salt.

24. A method according to Claim 21, wherein the pharmaceutical composition includes

approximately 5 to 12% by weight, based on the total weight of the composition, of a minoxidil or a minoxidil salt;

approximately 88 to 95% by weight of a solvent composition including

approximately 10 to 70% by weight of ethanol,

approximately 2.5 to 85% by weight of benzyl alcohol;

and less than 10% by weight, propylene glycol.

25. A pharmaceutical composition according to Claim 1, substantially as herein before described with reference to any one of the examples.

BAKER & BOTTS, L.L.P.
FILE NO.: RBH A 33447
PCT/USA

COMBINED DECLARATION AND POWER OF ATTORNEY

(Original, Design, National Stage of PCT, Divisional, Continuation or C-I-P Application)

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

This declaration is of the following type:

- [] original
- [] design
- [X] national stage of PCT.
- [] divisional
- [] continuation
- [] continuation-in-part (C-I-P)

the specification of which: *(complete (a), (b), or (c))*

(a) [X] is attached hereto.
(b) [ ] was filed on as Application Serial No. and was amended on *(if applicable)*.
(c) [ ] was described and claimed in PCT International Application No. filed on and was amended on *(if applicable)*.

Acknowledgement of Review of Papers and Duty of Candor

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of the subject matter claimed in this application in accordance with Title 37, Code of Federal Regulations § 1.56.

[ ] In compliance with this duty there is attached an information disclosure statement. 37 CFR 1.98.

Priority Claim

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT International Application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT International Application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application on which priority is claimed

(complete (d) or (e))

(d) [ ] no such applications have been filed.
(e) [X] such applications have been filed as follows:

PRIOR FOREIGN/PCT APPLICATION(S) FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION			
COUNTRY APPLICATION NO	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
			[ ] YES NO [ ]
			[ ] YES NO [ ]
			[ ] YES NO [ ]
ALL FOREIGN APPLICATION[S], IF ANY, FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION			
AUSTRALIA PP3107	22/04/1998		[X] YES NO [ ]
AUSTRALIA PCT/AU99/00294	20/04/1999		[X] YES NO [ ]
			[ ] YES NO [ ]

Claim for Benefit of Prior U.S. Provisional Application(s)

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

Provisional Application Number	Filing Date

Claim for Benefit of Earlier U.S./PCT Application(s) under 35 U.S.C. 120

(complete this part only if this is a divisional, continuation or C-I-P application)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose information as defined in Title 37, Code of Federal Regulations, § 1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

(Application Serial No)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No)	(Filing Date)	(Status) (patented, pending, abandoned)

Power of Attorney

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section

1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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100 200 300